Resective surgery prevents progressive cortical thinning in temporal lobe epilepsy

Galovic, Marian ; de Tisi, Jane ; McEvoy, Andrew W ; Miserocchi, Anna ; Vos, Sjoerd B ; Borzi, Giuseppe ; Cueva Rosillo, Juana ; Vuong, Khue Anh ; Nachev, Parashkev ; Duncan, John S ; Koepp, Matthias J

Abstract: Focal epilepsy in adults is associated with progressive atrophy of the cortex at a rate more than double that of normal ageing. We aimed to determine whether successful epilepsy surgery interrupts progressive cortical thinning. In this longitudinal case-control neuroimaging study, we included subjects with unilateral temporal lobe epilepsy (TLE) before (n = 29) or after (n = 56) anterior temporal lobe resection and healthy volunteers (n = 124) comparable regarding age and sex. We measured cortical thickness on paired structural MRI scans in all participants and compared progressive thinning between groups using linear mixed effects models. Compared to ageing-related cortical thinning in healthy subjects, we found progressive cortical atrophy on vertex-wise analysis in TLE before surgery that was bilateral and localized beyond the ipsilateral temporal lobe. In these regions, we observed accelerated annualized thinning in left (left TLE 0.0192 ± 0.0014 versus healthy volunteers 0.0032 ± 0.0013 mm/year, $P < 0.0001$) and right (right TLE 0.0198 ± 0.0016 versus healthy volunteers 0.0037 ± 0.0016 mm/year, $P < 0.0001$) presurgical TLE cases. Cortical thinning in these areas was reduced after surgical resection of the left (0.0074 ± 0.0016 mm/year, $P = 0.0006$) or right (0.0052 ± 0.0020 mm/year, $P = 0.0006$) anterior temporal lobe. Directly comparing the post- versus presurgical TLE groups on vertex-wise analysis, the areas of postoperatively reduced thinning were in both hemispheres, particularly, but not exclusively, in regions that were affected preoperatively. Participants who remained completely seizure-free after surgery had no more progressive thinning than that observed during normal ageing. Those with postoperative seizures had small areas of continued accelerated thinning after surgery. Thus, successful epilepsy surgery prevents progressive cortical atrophy that is observed in TLE and may be potentially neuroprotective. This effect was more pronounced in those who remained seizure-free after temporal lobe resection, normalizing the rate of atrophy to that of normal ageing. These results provide evidence of epilepsy surgery preventing further cerebral damage and provide incentives for offering early surgery in refractory TLE.

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Resective surgery prevents progressive cortical thinning in temporal lobe epilepsy: evidence for neuroprotection.

-- ONLINE SUPPLEMENT --

1. MRI acquisition protocol in epilepsy cohort

MRI data were acquired between August 2004 and March 2013 on the same 3T MRI GE Signa HDx scanner (GE, Milwaukee, WI, USA), with the same MRI image sequence used for analysis: coronal T1W 3D inversion-recovery fast spoiled gradient echo (IR-FSPGR) with repetition time / echo time / inversion time = 8.1 / 3.1 / 450 ms; field-of-view 187x240x240 mm; matrix 170x256x256, voxel dimensions 0.9x0.9x1.1mm.

2. Description of healthy volunteer cohorts

Healthy volunteer data in public repositories is mostly cross-sectional. A small number of longitudinal healthy volunteer datasets are available but they were mostly acquired as comparison for disease cohort of autism or dementia - i.e. the included volunteers are young (<20 years-old) or old (>70 years-old). We detected three publicly available cohorts of healthy volunteers aged between 20 to 70 years, having two 3T T1-weighted MRI scans on the same scanner at least 6 months apart.

Supplemental Table 1: *Healthy volunteer demographic by cohort*

	NMorphCH (n = 24)	PPMI (n = 48)	SLIM (n = 53)
Sex			
Female	10 (42%)	19 (40%)	47 (89%)
Male	14 (58%)	29 (60%)	6 (11%)
Age at baseline scan *(years)*	32 ± 9	56 ± 9	21 ± 1
Interval between scans *(years)*	1.7 ± 0.4	1.2 ± 0.4	2.1 ± 0.6

2.1 Neuromorphometry by Computer Algorithm Chicago (NMorphCH)

Number of volunteers: 24
Reference for Dataset: http://nunda.northwestern.edu/nunda/data/projects/NMorphCH
Obtained through: ShizConnect
Reference for ShizConnect: *Kogan A, Alpert K, Ambite JL, Marcus DS, Wang L. Northwestern University schizophrenia data sharing for SchizConnect: A longitudinal dataset for large-scale integration. Neuroimage 2016; 124: 1196–201.*
MR-acquisition: 3T Siemens TrioTim MRI scanner (Siemens Medical, Erlangen, Germany). A magnetization-prepared rapid gradient echo (MPRAGE) sequence was used to acquire high-resolution T1-weighted anatomical images (repetition time=2400 ms, echo time=3.16 ms, flip=8°, 256 x 256 matrix, 176 slices, slice thickness=1.0 mm, voxel size=1x1x1mm^3)

2.2 Parkinson Progression Marker Initiative (PPMI)

Number of volunteers: 48

Reference for Dataset: *Parkinson Progression Marker Initiative. The Parkinson Progression Marker Initiative (PPMI). Progress in Neurobiology 2011; 95: 629-35.*
MR-acquisition: Scans used for this longitudinal cohort were acquired on 3T Siemens TrioTim or Verio MRI scanners (Siemens Medical, Erlangen, Germany). A magnetization-prepared rapid gradient echo (MPRAGE) sequence was used to acquire high-resolution T1-weighted anatomical images (repetition time=2300, echo time=2.98, flip angle=9°, 240 x 256 matrix, 160-192 slices, slice thickness=1.0 mm, voxel size=1x1x1mm^3). The T1 acquisition protocol followed ADNI-3 sequence parameter recommendations: http://adni.loni.usc.edu/wp-content/uploads/2017/07/ADNI3-MRI-protocols.pdf
Detailed description of MR-acquisition protocol can be found in the PPMI MRI Technical Operations Manual: http://www.ppmi-info.org/wp-content/uploads/2017/06/PPMI-MRI-Operations-Manual-V7.pdf

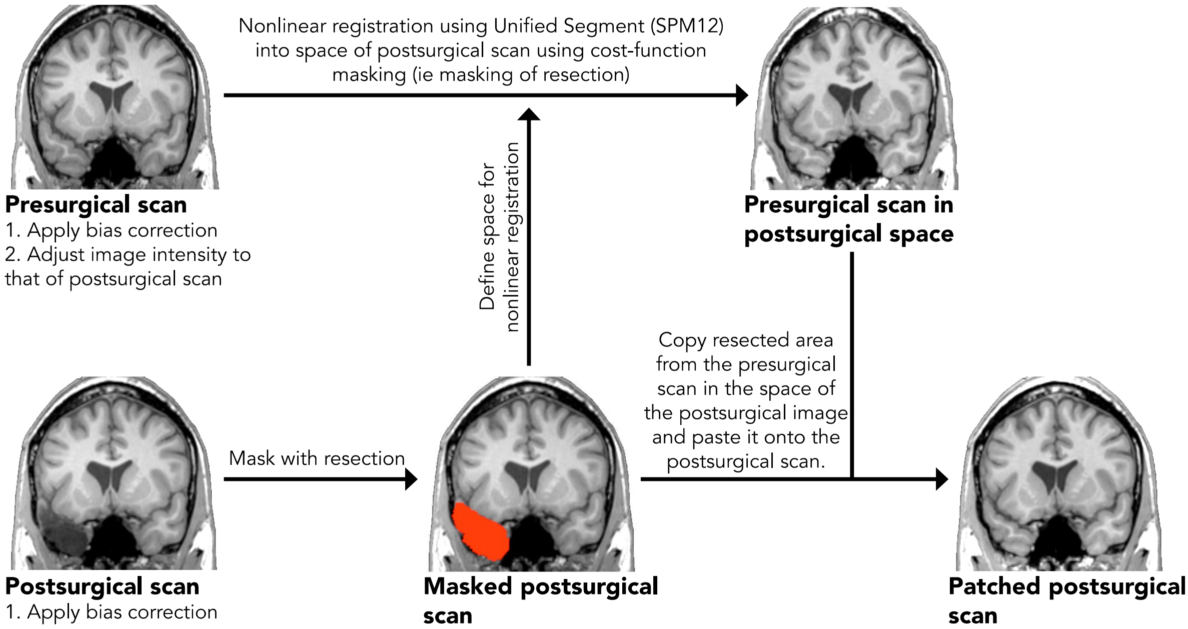
2.3 Southwest University Longitudinal Imaging Multimodal study (SLIM)
Number of volunteers: 53
Reference for Dataset: *Liu W, Wei D, Chen Q, et al. Longitudinal test-retest neuroimaging data from healthy young adults in southwest China. Sci Data 2017; 4: 170017.*
MR-acquisition: 3T Siemens Trio MRI scanner (Siemens Medical, Erlangen, Germany). A magnetization-prepared rapid gradient echo (MPRAGE) sequence was used to acquire high-resolution T1-weighted anatomical images (repetition time = 1900 ms, echo time = 2.52 ms, inversion time = 900 ms, flip angle = 9 degrees, resolution matrix = 256 x 256, slices = 176, thickness = 1.0 mm, voxel size=1x1x1mm^3.

3. MRI preprocessing procedure

3.1 Extraction of resection masks
We extracted surgical resection masks with an automated procedure, as described previously (*Galovic M, Baudracco I, Wright-Goff E, et al. Association of Piriform Cortex Resection With Surgical Outcomes in Patients With Temporal Lobe Epilepsy. JAMA Neurol. 2019;76(6):690-700*). This approach was based on a previously proposed lesion-segmentation algorithm (*Seghier ML, Ramlackhansingh A, Crinion J, Leff AP, Price CJ. Lesion identification using unified segmentation-normalisation models and fuzzy clustering. Neuroimage 2008; 41: 1253-66*).
We used pre- and postsurgical scans in every subject to extract the difference between these two scans using the unified segmentation-normalization procedure implemented in SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) with an empirical prior for an atypical tissue class (i.e. the resection). The procedure was iterated twice to refine the resection mask and the mask was nonlinearly coregistered into the space of the presurgical image. All obtained masks were checked by an investigator (MG) and if necessary manually adjusted. To correct for different head sizes, resection volumes were estimated after spatially normalizing them into a standard template with deformations estimated using the presurgical image.

3.2 Spatial normalization
Preprocessing of postsurgical scans can be problematic due to the lack of appropriate normalisation templates and brain shift caused by surgery. We aimed to minimise the impact of the resections using a novel procedure that shares its methodological concepts with "enantiomorphic normalisation", proposed by Nachev and colleagues in 2008. In the enantiomorphic procedure, a unilateral lesion is "patched" by copying and pasting the corresponding area from the contralateral hemisphere. In this manner, the lesion is made to look like healthy brain tissue. Image preprocessing of patched images is more accurate and efficient and does not violate the preprocessing assumptions. After spatial preprocessing the patch is masked, in order not to influence further analyses.
In our study, we obtained presurgical scans for all subjects from the postsurgical group. Thus, we decided to patch the resected area on the postsurgical scan using the corresponding area from the presurgical scan. In this manner, we effectively mimicked the behaviour of presurgical scans during spatial preprocessing.
In order to achieve this (Supplemental Figure 1), we first bias corrected both pre- and postsurgical scans and aligned their image intensities. Next, the postsurgical scan was masked with the resection mask obtained using a previously described procedure (see Online Supplement section 3.1). The masked postsurgical scan was nonlinearly registered into the space of the presurgical image using cost-function masking, as proposed by Brett et al. 2001. Nonlinear registration of pre- and postsurgical images remains highly accurate despite the presence of a lesion, because of the high between-scan similarities acquired in the same subject. Next, we applied the inverse of these deformations to the presurgical scan to transform it into the space of the postsurgical image. Lastly, we copied and pasted a patch corresponding to the resection mask with smoothed edges from the pre- onto the postsurgical scan. This produced a patched postsurgical scan that would behave similarly to the

presurgical scan during image preprocessing. Preprocessing was done using SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/).



Supplemental Figure 1: *Illustration of patching procedure during image preprocessing.*

3.3 Estimation of cortical thickness

All subjects were preprocessed using the same fully automated, validated, and reliable (*see references below*) Computational Anatomy Toolbox (CAT12, http://www.neuro.uni-jena.de/cat/) running in SPM12 (Wellcome Centre for Human Neuroimaging), as described previously (*Galovic M, van Dooren VQH, Postma T, et al. Progressive Cortical Thinning in Patients With Focal Epilepsy. JAMA Neurol. July 2019*).

Cortical thickness was estimated using the projection-based thickness method, that was previously validated using spherical and brain phantoms confirming accurate measurements under a wide set of parameters for several thickness levels (Dahnke *et al.*, 2013). The CAT12 toolbox showed excellent test-retest reliability (R^2 = 0.986) and was validated against other cortical surface reconstruction methods, showing fewer thickness measurement errors than comparable approaches (Righart *et al.*, 2017; Seiger *et al.*, 2018).

References:

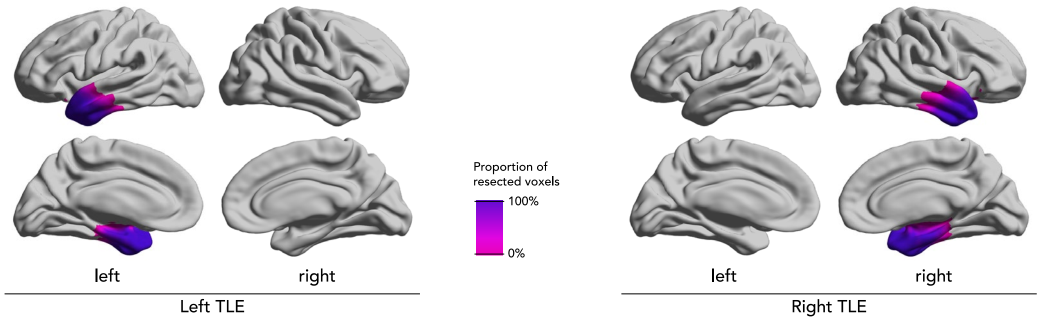
- Dahnke R, Yotter RA, Gaser C. Cortical thickness and central surface estimation. *Neuroimage*. 2013;65:336-348. doi:10.1016/j.neuroimage.2012.09.050.
- Righart R, Schmidt P, Dahnke R, et al. Volume versus surface-based cortical thickness measurements: A comparative study with healthy controls and multiple sclerosis patients. *PLoS ONE*. 2017;12(7):e0179590. doi:10.1371/journal.pone.0179590.
- Seiger R, Ganger S, Kranz GS, Hahn A, Lanzenberger R. Cortical Thickness Estimations of FreeSurfer and the CAT12 Toolbox in Patients with Alzheimer's Disease and Healthy Controls. *J Neuroimaging*. May 2018. doi:10.1111/jon.12521.

All data were quality controlled according to procedures implemented in CAT12 and scans with misalignment, misregistration, or inaccurate thickness estimation were excluded.

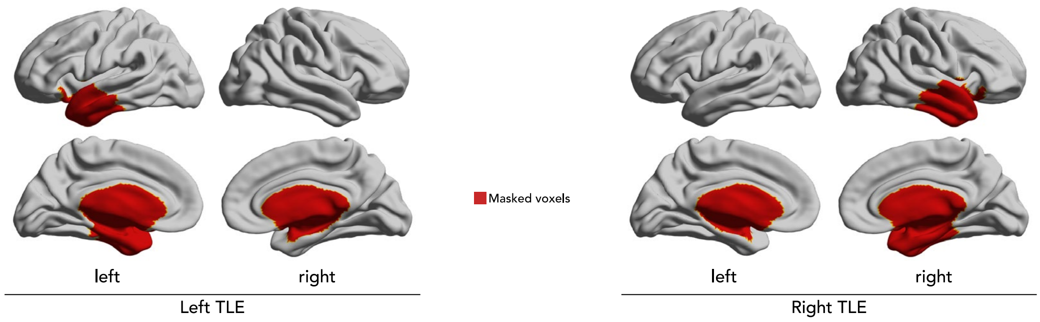
3.4 Mean extent of resection and masking

The mean extent of surgical resections is displayed in Supplemental Figure 2A. As a next step, we created a mask including voxels that were resected in at least 10% of subjects and dilated the mask by a safety margin of 3mm. We also included the interhemispheric cut in the mask. Separate masks were created for left and right temporal lobe epilepsy (TLE). The masks were then transformed from voxel space into surface space using commands in the CAT12 toolbox (Supplemental Figure 2B).

A Mean surgical resection extent



B Mask for dilated resection and interhemispheric cut



Supplemental Figure 2: *(A) Mean extent of standard anterior temporal lobe resection in left and right temporal lobe epilepsy (TLE). (B) Mask created out of dilated resection and interhemispheric cut.*

3.5 Masking of the resection

All postsurgical scans were masked with the individual resection mask dilated by 3mm to remove the patched areas and to apply a safety margin for potential structural alterations in the regions immediately surrounding the resection (Online Supplement section 3.4). Similarly, all presurgical and healthy volunteer scans were masked with the respective left or right temporal mean resection mask with a safety margin of 3mm, when comparisons with postsurgical scans were performed. Cortical thickness maps were smoothed with a 15-mm surface-based kernel.

4. Baseline characteristics in left and right TLE

There were no differences in baseline characteristics between patients with left and right TLE (Supplemental Table 2).

Supplemental Table 2: *Baseline characteristics in patients with left and right TLE*

	Left TLE (n = 47)	Right TLE (n=38)	P value
Gender			
Female	26 (55%)	25 (67%)	0.38
Male	21 (48%)	13 (34%)	
Age			
Age mid-scan *(years)*	40 ± 12	39 ± 12	0.88
Age at seizure onset *(years)*	14 ± 10	15 ± 11	0.77
Age at surgery *(years)*	40 ± 12	40 ± 12	0.99
Duration of epilepsy at surgery *(years)*	26 ± 14	25 ± 13	0.82
Presurgical seizures			
Focal aware	26 (55%)	16 (42%)	0.28
Focal impaired awareness	45 (96%)	37 (97%)	1.00
Focal to bilateral tonic-clonic	37 (79%)	28 (74%)	0.62
Focal impaired awareness frequency *(per month)*	10 ± 9	33 ± 162	0.40
Focal to bilateral tonic-clonic frequency *(per month)*	0.9 ± 2.2	0.4 ± 1.2	0.29
Pathology			
Hippocampal sclerosis	35 (75%)	29 (76%)	1.00
Dysembryoplastic neuroepithelial tumor	6 (13%)	3 (8%)	0.73
Cavernoma	1 (2%)	2 (5%)	0.58
Other	9 (19%)	7 (18%)	1.00
Surgical outcome			
Seizure free after surgery (ILAE Class Ia)	19 (40%)	16 (42%)	0.54
Other			
Number of antiepileptic drugs at surgery	3 ± 1	2 ± 1	0.38
History of a precipitating injury*	5 (11%)	2 (5%)	0.45
History of childhood febrile convulsions	10 (21%)	3 (8%)	0.13
History of depression	15 (32%)	13 (35%)	0.82
History of psychosis	4 (9%)	3 (8%)	1.00
History of anxiety disorder	7 (15%)	5 (14%)	1.00

Data displayed as N (%) or mean ± standard deviation. Data analysed with Fisher's exact test for nominal variables or with the independent T-Test for scalar variables. * Most commonly reported precipitating injuries were a history of meningitis or traumatic brain injury.

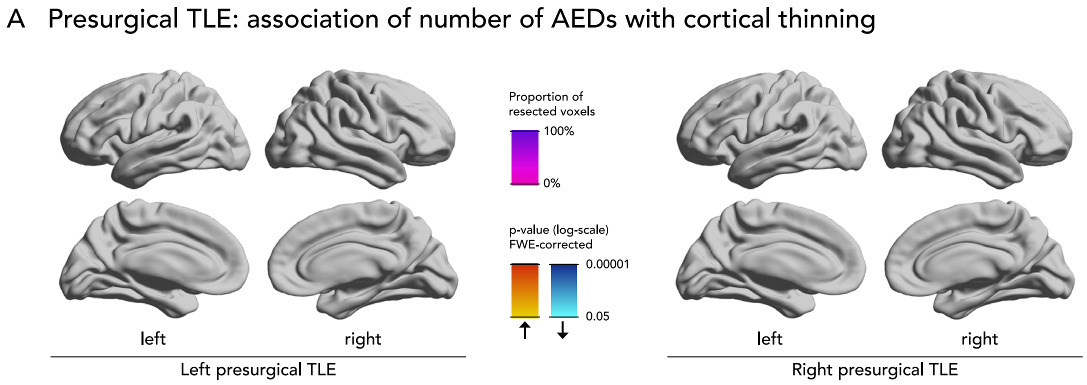
5. Coefficient of variation

The coefficient of variation of cortical thickness measurements was lower in healthy volunteers (4.0%) and in the postsurgical patient group (5.1%) compared to the presurgical patient group (5.8%). The increased variability in epilepsy patients compared to healthy volunteers is most likely explained by biological variability, i.e. differences in severity and duration of epilepsy.

This demonstrates that there was smaller data variability in the healthy volunteer cohort and in the postsurgical cohort than in the presurgical cohort. The greater the variability the lesser the accuracy for detecting cortical thinning: that the presurgical group nonetheless showed *greater* thinning compared to the postsurgical group shows this is highly unlikely to have resulted from differences in variability, for that would cause an effect in the *opposite* direction. Thus, our findings cannot be explained by a reduced sensitivity to detect cortical thinning in postsurgical compared to presurgical epilepsy patients.

6. Association of antiepileptic drugs with cortical thinning

We assessed the association of number of antiepileptic drugs (AEDs) with progressive cortical thinning in both pre- and postsurgical patient groups. We followed a similar statistical procedure as for the analyses in the main manuscript. We did not find any significant association of AED load with cortical thinning before or after surgery (Supplemental Figure 3).



Supplemental Figure 3: *Association of number of AEDs at baseline scan with cortical thinning before (A) or after (B) temporal lobe resection in left and right TLE.*

7. Findings in a presurgical subgroup with short interscan intervals

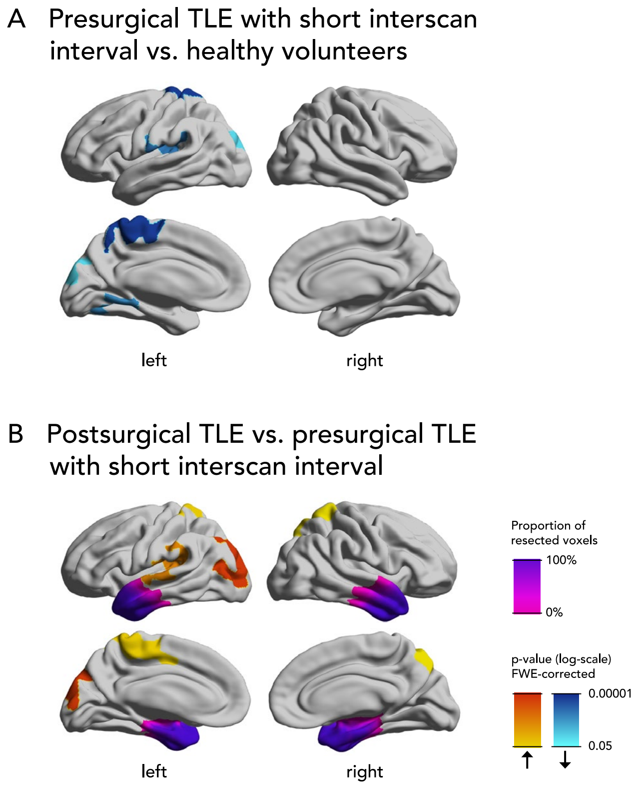
The presurgical group had a longer interscan interval (28 ± 16 months) compared to the postsurgical group (14 ± 11 months). Although all analyses were adjusted for lengths of interscan intervals, we performed a sensitivity analysis in a presurgical subgroup with short interscan intervals.

In this sensitivity analysis, we included presurgical cases with an interval between the scans shorter than 2 years. The 13 cases in this subgroup had an interval of 15 ± 5 months, comparable with the postsurgical group. Because of the small number of subjects we did not split the analyses into left and right TLE. Thus, we compared progressive cortical thinning in the whole subgroup of presurgical patients with short interscan interval against healthy volunteers (Supplemental Figure 4A) and postsurgical cases (Supplemental Figure 4B). We used a bilateral resection mask because this group included both left- and right-sided resections.

Compared to healthy volunteers (Supplemental Figure 4A), the presurgical subgroup had progressive cortical thinning in the left paracentral lobule and superior frontal gyrus (1002 vertices, $p<0.0001$), insular cortex and postcentral gyrus (968 vertices, $p=0.0002$), lingual and fusiform gyri (623 vertices $p=0.0004$), and superior parietal cortex (500 vertices, $p=0.01$).

Comparing the postsurgical group to the presurgical subgroup (Supplemental Figure 4B), there was postoperatively reduced thinning in the left superior and inferior parietal cortex (1659 vertices, $p<0.0001$), left superior temporal and supramarginal gyri and insular cortex (1466 vertices, $p=0.0007$), left paracentral lobule and superior frontal gyrus (1041 vertices, $p=0.01$), and right superior postcentral gyrus and superior parietal cortex (849 vertices, $p=0.02$).

To conclude, we demonstrated in a presurgical subgroup with short interscan intervals progressive cortical thinning compared to healthy controls. We showed that thinning was significantly less postoperatively. Thus, we replicated the key findings of the main study, making it unlikely that the results can be explained by a difference in interscan intervals between the pre- and postsurgical groups.



Supplemental Figure 4: *Comparison of progressive cortical thinning in a subgroup of presurgical cases with short interscan intervals with healthy volunteers (A) and the postsurgical group (B).*

Resective surgery prevents progressive cortical thinning in temporal lobe epilepsy.

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Running title: Epilepsy surgery prevents neurodegeneration

Abstract

Focal epilepsy in adults is associated with progressive atrophy of the cortex at a rate more than double that of normal aging. We aimed to determine whether successful epilepsy surgery interrupts progressive cortical thinning. In this longitudinal case-control neuroimaging study, we included people with unilateral temporal lobe epilepsy (TLE) before (n=29) or after (n=56) anterior temporal lobe resection and healthy volunteers (HV, n=124) comparable regarding age and sex. We measured cortical thickness on paired structural MRI scans in all participants and compared progressive thinning between groups using linear mixed effects models. Compared to aging-related cortical thinning in healthy volunteers, we found progressive cortical atrophy on vertex-wise analysis in TLE before surgery that was bilateral and localized beyond the ipsilateral temporal lobe. In these regions, we observed accelerated annualized thinning in left (left TLE 0.0192 ± 0.0014 vs. HV 0.0032 ± 0.0013 mm/year, p<0.0001) and right (right TLE 0.0198 ± 0.0016 vs. HV 0.0037 ± 0.0016 mm/year, p<0.0001) presurgical TLE cases. Cortical thinning in these areas was reduced after surgical resection of the left (0.0074 ± 0.0016 mm/year, p=0.0006) or right (0.0052 ± 0.0020 mm/year, p=0.0006) anterior temporal lobe. Directly comparing the post- vs. presurgical TLE groups on vertex-wise analysis, the areas of postoperatively reduced thinning were in both hemispheres, particularly, but not exclusively, in regions that were affected preoperatively. Participants who remained completely seizure-free after surgery had no more progressive thinning than that observed during normal aging. Those with postoperative seizures had small areas of continued accelerated thinning after surgery. Thus, successful epilepsy surgery prevents progressive cortical atrophy that is observed in TLE and may be potentially neuroprotective. This effect was more pronounced in those who remained seizure-free after temporal lobe resection, normalising the rate of atrophy to that of normal aging. These results

provide evidence of epilepsy surgery preventing further cerebral damage and provide incentives for offering early surgery in refractory TLE.

Keywords: epilepsy, seizures, MRI, surgery, neurodegeneration

Abbreviations:

AED = Antiepileptic drug

ANOVA = Analysis of variance

CAT12 = Computational Anatomy Toolbox 12

CoV = Coefficient of variation

FEW = Family-wise error

ROI = Region of interest

SPM12 = Statistical Parametric Mapping 12

TLE = Temporal lobe epilepsy

Introduction

Emerging evidence from imaging (Alvim *et al.*, 2016; Bernhardt *et al.*, 2009; Caciagli *et al.*, 2017; Galovic, van Dooren, *et al.*, 2019; Govil-Dalela *et al.*, 2018; R. S. N. Liu *et al.*, 2003), psychometric (Hermann *et al.*, 2006; Jokeit and Ebner, 1999; Thompson and Duncan, 2005), and electroencephalographic (Gollwitzer *et al.*, 2017; Hughes, 1985) data suggests that epilepsy is a progressive rather than a static disease. In clinical terms, Sir William Gowers hypothesised that "seizures beget seizures" more than 130 years ago (Gowers, 1881), but the notion of clinical progression remains controversial (Cole, 2000; Sutula *et al.*, 2003).

People with epilepsy showed a greater rate of cognitive decline compared to healthy people (Hermann *et al.*, 2006; Thompson and Duncan, 2005). One third of those with initially unilateral epileptic discharges on EEG progressed to bilateral discharges on subsequent recordings (Gollwitzer *et al.*, 2017), with a progression rate of around 1% per year (Hughes, 1985). Adults with epilepsy are well known to show widespread cortical thinning beyond the area typically considered as the epileptic focus (Whelan *et al.*, 2018). Cortical thinning has not been shown in paediatric epilepsy patients and in siblings of patients with epilepsy, which may suggest that neurodegeneration is the consequences of a protracted disease process and, thus, may be preventable (Adler *et al.*, 2018; Long *et al.*, 2020).

We recently proposed serial structural magnetic resonance imaging (MRI) as a quantifiable, reproducible, and biologically valid (Cardinale *et al.*, 2014) biomarker of progressive neurodegeneration in epilepsy (Fischl and Dale, 2000; Galovic, van Dooren, *et al.*, 2019). We showed that cortical thinning in epilepsy advances at a rate more than double that of normal aging, particularly during the first five years after the onset of seizures (Galovic, van Dooren, *et al.*, 2019). Similar observations were made in a large number of longitudinal neuroimaging studies assessing changes in brain structure (Alvim *et al.*, 2016; Bernhardt *et al.*, 2009; Caciagli *et al.*, 2017; R. S. N. Liu *et al.*, 2003) or cerebral metabolism

(Govil-Dalela *et al.*, 2018). Several but not all studies observed that progressive changes were not related to seizure frequency, suggesting that neurodegeneration and loss of grey matter might be the manifestation of a widespread pathological process affecting neuronal networks in epilepsy that might continue even in the absence of overt seizures (Alvim *et al.*, 2016; Galovic, van Dooren, *et al.*, 2019; R. S. N. Liu *et al.*, 2003).

Despite this mounting evidence it remains unknown how to prevent progressive neurodegeneration in epilepsy. Current antiepileptic drugs (AEDs) are merely seizure suppressants and have not shown disease-modifying effects in humans (Marson *et al.*, 2005). In contrast, successful epilepsy surgery can lead to disease-modification and cure, ie. long-term freedom from seizures after withdrawing medication (de Tisi *et al.*, 2011). Epilepsy surgery remains, however, underutilised with a mean delay of 18 to 23 years between the onset of seizures and referral for surgery (Haneef *et al.*, 2010). It is unknown whether epilepsy surgery affects progressive neurodegeneration in epilepsy. If so, there would be an additional incentive to identify surgical candidates early and to reduce delays in offering surgery.

Here, we aimed to determine whether epilepsy surgery prevents further progressive neurodegeneration in refractory focal epilepsy. We assessed pre- and postoperative progressive cortical thinning in people with temporal lobe epilepsy (TLE) undergoing surgery and compared it with aging-related thinning in a group of healthy volunteers.

Materials and methods

Participants

From an ongoing single-centre prospective cohort study of long-term outcome after epilepsy surgery (de Tisi *et al.*, 2011), we identified consecutive individuals with medically refractory unilateral TLE who underwent standard anterior temporal lobe resections from 1st

January 2004, through 31st December 2016. We included those who had (i) serial high-resolution T1-weighted MRI scans at least 6 months apart performed on the same scanner before (presurgical group) or after (postsurgical group) surgery, (ii) underwent surgery by the same neurosurgeon (A.W.M.) and (iii) had at least one year of postoperative follow up. The subjects did not have a history of dementia, stroke, neurodegenerative conditions, white matter lesions, or other relevant active neurological disorders. All subjects with a pair of postoperative scans were additionally required to have had a presurgical scan to support MRI spatial preprocessing. Patients with MRI scans of insufficient quality (i.e. patient movement or technical artefacts) were excluded.

Diagnosis of TLE was made by a multidisciplinary epilepsy team evaluation based on clinical history, neurologic examination, seizure semiology, long-term video-EEG telemetry, MRI, and neuropsychological and psychiatric assessments. Fluorodeoxyglucose positron emission tomography, ictal single-photon emission tomography, and intracranial EEG telemetry were used if needed to clarify the epileptogenic zone. Patients with concordant findings, including those with nonlesional MRI, were deemed potential surgical candidates and their anterior temporal lobe was resected as described below. Seizure outcome was prospectively assessed annually using a standard surgery outcome classification (Wieser *et al.*, 2001). Patients were considered to be seizure free only if they never experienced seizures or auras throughout follow-up (class Ia outcome), not considering seizures within the first week after surgery.

Repeat preoperative imaging is frequently performed at our centre for presurgical planning (mean 43 ± 22 and 15 ± 12 months before surgery in included subjects, mean interscan interval 28 ± 16 months). Serial postoperative imaging is routinely performed at our centre ≥3 months and ≥12 months after surgery (mean 4 ± 1 and 18 ± 11 months in included subjects, mean interscan interval 14 ± 11 months). MRIs in patients were acquired on a 3T

GE Signa HDx scanner using a coronal T1-weighted 3D inversion-recovery fast spoiled gradient echo sequence and 0.9x0.9x1.1mm voxel dimensions (for detailed MRI acquisition protocols see Online Supplement, sections 1 and 2).

The study was classified by the Institutional Review Board as a service evaluation involving further anonymised analysis of previously acquired data that did not require individual participant consent.

As described previously (Galovic, van Dooren, *et al.*, 2019), we compared the epilepsy data to an age- and sex-matched comparison group of healthy volunteers from three publicly available anonymised longitudinal MRI datasets (see Online Supplement section 2) (Kogan *et al.*, 2016; W. Liu *et al.*, 2017; Parkinson Progression Marker Initiative, 2011). Healthy volunteers were aged between 20 and 70 years, each having two high-resolution T1-weighted scans at least 6 months apart (mean interval 20 ± 8 months).

Neurosurgical procedure

The standard neurosurgical procedure consisted in identifying the temporal horn entering from the collateral sulcus to minimise damage to the optic radiation and removing the temporal pole *en bloc*. This was followed by debulking of the amygdala, resection of the piriform cortex and *en bloc* resection of the hippocampus with a posterior resection margin at the mid-brainstem level. The resection of the parahippocampal gyrus is also taken to the same level as the hippocampus.

Typically, the anterior–posterior extent of the temporal lobe resection as measured from the temporal pole to the posterior margin of resection is 30% and 35% of the distance from the temporal pole to the occipital pole after left and right anterior temporal lobe resection, respectively. As surgery was performed by the same operator there was little variation of the temporal neocortical extent of the resection.

MRI preprocessing

The MRI preprocessing procedure is described in detail in the Online Supplement, section 3. In brief, we firstly extracted surgical resection masks with an automated procedure, as described previously (Galovic, Baudracco, *et al.*, 2019). The masks were manually checked by an investigator (MG) for segmentation errors and adjusted if necessary.

Secondly, preprocessing of postsurgical scans can be problematic due to the lack of appropriate normalisation templates and brain shift caused by surgery. We aimed to minimise the impact of the resection by patching the resected area with the corresponding region from the presurgical scan. This shares the concept with enantiomorphic normalisation (i.e. patching a unilateral lesion with the unaffected contralateral side) that was shown to effectively prevent bias in scans with large lesions (Nachev *et al.*, 2008). In this manner, we effectively mimicked the behaviour of a presurgical scan during spatial preprocessing. A detailed description and example are shown in the Online Supplement section 3.2.

Thirdly, cortical thickness was estimated using the fully automated (Dahnke *et al.*, 2013), validated (Dahnke *et al.*, 2013; Righart *et al.*, 2017; Seiger *et al.*, 2018), and reliable (Dahnke *et al.*, 2013; Seiger *et al.*, 2018) Computational Anatomy Toolbox (CAT12) running in SPM12 (Wellcome Centre for Human Neuroimaging), as described previously (Galovic, van Dooren, *et al.*, 2019) (Online Supplement section 3.3). All data were quality controlled according to procedures implemented in CAT12 and scans with misalignment, misregistration, or inaccurate thickness estimation were excluded.

Lastly, all postsurgical scans were masked with the resection mask dilated by 3mm to remove the patched areas and to apply a safety margin for potential structural alterations in the regions immediately surrounding the resection (Online Supplement section 3.5). Similarly, all presurgical and healthy volunteer scans were masked with the respective left or right temporal mean resection mask with a safety margin of 3mm, when comparisons with postsurgical scans were performed. Cortical thickness maps were smoothed with a 15-mm surface-based kernel.

To validate the performance of the preprocessing procedure, we determined the correspondence of the processed images with the normalization template using Dice coefficients (Dice, 1945). No differences were noted in the normalization accuracy between pre- and postsurgical scans and healthy volunteers (0.96 ± 0.02 vs. 0.96 ± 0.01 vs. 0.95 ± 0.03, $p=0.18$).

Statistical analysis

Categorical variables are displayed as N (%) and were analysed with Fisher's exact test. Continuous variables are displayed as mean ± standard deviation and were analysed with one-way analysis of variance (ANOVA). Calculations were carried out in SPSS (IBM Corp, Version 24.0).

Cortical thinning within regions of interest (ROI) was determined in areas that showed significant vertex-wise cortical thinning in left or right TLE before surgery (**Figure 1A** left and right, different ROIs were defined for left and right TLE). The rationale was to determine whether progressive cortical thinning changed after surgery in the areas that showed significant thinning before surgery.

Cortical thickness measurements were analysed with SurfStat within MATLAB (http://www.math.mcgill.ca/keith/surfstat) using vertex-wise and ROI-wise approaches. We fitted linear mixed-effects models, a flexible framework for longitudinal analysis of multiple repeated measurements per subject with irregular measurement intervals. In order to test for differences between groups (e.g. pre- *vs.* postsurgical patients) on change of cortical thickness over time, we tested for a main effect of an interaction between the *group-allocation* and *age at scan*, correcting for a random effect of *subject* and fixed effects of *age* *at scan*, *sex*, and *group*. With this approach, we were able to test for within-subject thickness changes over time while correcting for baseline demographic differences and for different inter-scan intervals. We report findings at $p<0.05$ corrected for multiple comparisons using random field theory for nonisotropic images on a cluster level (Worsley *et al.*, 1999) or using Bonferroni correction for ROI values of annualised cortical thinning. Annualized cortical thinning in ROIs was estimated as the predicted slope of the linear regression lines from the mixed effects models.

Data availability

The scripts used for data preprocessing and anonymized data are available upon reasonable request.

Results

The studied cohorts involved 418 scans in 209 subjects. We included 29 TLE patients (16 [55%] left TLE) with paired presurgical scans and 56 TLE patients (31 [55%] left TLE) with paired postsurgical scans, all of whom underwent unilateral anterior temporal lobe removal. Eight patients (all left TLE) were included in both groups because they had paired pre- and postsurgical scans. We compared the pre- and postsurgical patient groups with 124 healthy volunteers that were comparable for age (38 ± 11 vs. 39 ± 12 vs. 38 ± 17 years, $p=0.88$) and sex (52% vs. 64% vs. 61% female, $p=0.51$). Except for differences in interscan interval, there were no differences between the pre- and postsurgical groups in baseline characteristics (**Table 1**). There were no differences in baseline characteristics between patients with left and right TLE (Online Supplement section 4).

TLE vs. normal aging

Compared to aging-related cortical thinning in healthy volunteers, left presurgical TLE (**Figure 1A left**) showed accelerated thinning in the left superior pre- and postcentral gyri (1575 vertices, $p<0.0001$), left cuneus, precuneus and lingual gyrus (1087 vertices, $p<0.0001$), left inferior parietal lobule (548 vertices, $p=0.0005$), left rostral medial and inferior frontal gyri (397 vertices, $p=0.007$) and right superior pre- and postcentral gyri (511 vertices, $p=0.03$). Right presurgical TLE (**Figure 1A right**) showed more thinning in the left inferior pre- and postcentral gyri (918 vertices, $p=0.0002$), right superior pre- and postcentral gyri (822 vertices, $p=0.0004$), and left superior pre- and postcentral gyri (691 vertices, $p=0.002$). Presurgical cortical thinning in left or right TLE was not associated with seizure frequency.

Left postsurgical TLE (**Figure 1B left**) showed greater thinning than healthy volunteers in the left posterior fusiform, lingual and cingulate gyri (1705 vertices, $p<0.0001$) and left precuneus (290 vertices, $p=0.05$), but these areas were smaller than those observed in the presurgical group. Conversely, progressive cortical thickening was observed in the right supramarginal gyrus and superior parietal lobule (512 vertices, $p=0.02$). Progressive atrophy in right postsurgical TLE did not differ from healthy volunteers (no significant clusters, **Figure 1B right**). Postsurgical cortical thinning in left or right TLE was not associated with resection volume.

Presurgical left TLE patients had more cortical thinning per year (0.0192 ± 0.0014 mm/year) compared to healthy volunteers (0.0032 ± 0.0013 mm/year, $p<0.0001$) and to postsurgical left TLE patients (0.0074 ± 0.0016 mm/year, $p=0.0006$, **Figure 1C left**) in the regions that were significantly affected in left TLE before surgery (**Figure 1A left**). Similarly, presurgical right TLE patients had more annualised cortical thinning (0.0198 ± 0.0016 mm/year) compared to healthy volunteers (0.0037 ± 0.0016 mm/year, $p<0.0001$) and to postsurgical right TLE patients (0.0052 ± 0.0020 mm/year, p=0.0006, **Figure 1C right**) in the regions that were significantly affected in right TLE before surgery (**Figure 1A right**).

Post- vs. presurgical TLE

Directly comparing progressive structural changes before and after left temporal surgery (**Figure 2A**), the postsurgical group showed less progressive atrophy in large clusters involving the right posterior temporal, parietal and occipital cortices (6196 vertices, p<0.0001), right inferior and opercular frontal and parietal cortices (3715 vertices, p<0.0001), right anterior and middle cingulate gyri (1412 vertices, p<0.0001), left superior pre- and postcentral gyri (842 vertices, p<0.0001), and left superior parietal lobule (415 vertices, p=0.007).

In right TLE (**Figure 2B**), the postsurgical group showed less progressive cortical thinning in the right paracentral lobule and postcentral gyrus (665 vertices, p=0.0007) and left anterior insular cortex (550 vertices, p=0.01) compared to the presurgical group.

We performed a secondary analysis in 8 patients with left TLE, who had both pre- and postsurgical scans (**Figure 3**). Such a within-subject analysis eliminates the influence of between group differences and other confounders on the results because the pre- and postsurgical epochs are compared within the same individuals. After surgery, there was less progressive cortical thinning in large clusters involving the right posterior temporal, parietal and occipital cortices (5458 vertices, p<0.0001), right supramarginal gyrus (1103 vertices, p<0.0001), right cingulate gyrus (1023 vertices, p<0.0001), right frontal opercular cortex (631 vertices, p=0.004), and right precentral and superior frontal gyri (394 vertices, p=0.008). We also found more progressive cortical thinning after surgery in the left supramarginal gyrus (547 vertices, p=0.0003) and superior temporal gyrus (404 vertices, p=0.009).

Influence of surgical outcome

Compared to normal aging in healthy volunteers, non-seizure-free postsurgical left TLE patients (**Figure 4A left**) had more progressive cortical thinning in the left lingual and posterior cingulate gyri (1037 vertices, $p<0.0001$). Non-seizure-free postsurgical right TLE patients (**Figure 4A right**) had accelerated cortical thinning in the left lateral occipital cortex (202 vertices, $p=0.05$).

Conversely, seizure-free postsurgical left TLE patients (**Figure 4B left**) did not differ from normal aging in healthy volunteers (no significant clusters). Seizure-free postsurgical right TLE patients (**Figure 4B right**) did not show any accelerated cortical thinning compared to healthy volunteers, but they additionally showed focal cortical thickening in the right postcentral gyrus (809 vertices, $p=0.0003$).

Sensitivity analyses

We performed several sensitivity analyses. We measured the coefficient of variation (CoV) of cortical thickness measurements in all groups (see Online Supplement, section 5). The CoV was lower in healthy volunteers (4.0%) and in the postsurgical patient group (5.1%) compared to the presurgical patient group (5.8%).

To address the influence of AEDs on progressive thinning, we assessed the association of number of AEDs with progressive thinning and did not find any association before or after surgery (see Online Supplement, section 6).

Because the preoperative group had longer interscan intervals compared to the postoperative group, we performed subgroup analyses (see Online Supplement, section 7) in a presurgical subgroup with short interscan intervals (15 ± 5 months) that were comparable to the postsurgical group (14 ± 11 months). In this subgroup we confirmed accelerated cortical thinning in presurgical patients with epilepsy compared to healthy volunteers. We also confirmed that cortical thinning was significantly lessened postoperatively.

Discussion

We assessed progressive cortical thinning before and after anterior temporal lobe resection in a well-characterized cohort of unilateral TLE patients. We used a robust and reliable longitudinal neuroimaging pipeline to compare progressive changes in TLE before *vs.* after surgery and to aging-related thinning in matched healthy volunteers. We confirmed that individuals with TLE had accelerated cortical thinning prior to surgery in areas extending beyond the epileptic focus. We demonstrated that the rate of progressive thinning is significantly reduced during the first year after surgical removal of the anterior temporal lobe. The effect of surgery correlated with postoperative outcome and was more pronounced in those who remained completely seizure free. Postoperatively seizure-free subjects had no more annualized thinning than that observed during normal aging. Our results suggest that successful epilepsy surgery in the temporal lobe could have a neuroprotective effect and might prevent ongoing neurodegeneration in TLE, providing further support for the early utilization of surgery in refractory epilepsy.

Cortical thinning is a morphometric marker of neuronal loss and neurodegeneration that can be reliably and noninvasively assessed using structural MRI (Cardinale *et al.*, 2014; Fischl and Dale, 2000). Longitudinal neuroimaging is a statistically powerful framework (Steen *et al.*, 2007) to assess progressive neurodegeneration. Here, we showed that refractory TLE is associated with accelerated cortical thinning with a rate more than twice that of normal aging in the affected areas (**Figure 1C**), as has been characterised by us and others in previous studies (Alvim *et al.*, 2016; Bernhardt *et al.*, 2009; Caciagli *et al.*, 2017; Galovic, van Dooren, *et al.*, 2019; Govil-Dalela *et al.*, 2018; R. S. N. Liu *et al.*, 2003). This rate is particularly striking considering the mean 25-year duration of epilepsy in our cohort (**Table 1**), suggesting that even chronic refractory focal epilepsy can lead to ongoing neuronal damage. The affected areas were bilateral and spread beyond what is traditionally considered the epileptic focus (**Figure 1A**), reinforcing the concept of focal epilepsy as a network disorder. These regions may be particularly vulnerable because of their high interconnection with the epileptogenic zone in the temporal lobe (Galovic, van Dooren, *et al.*, 2019).

Proposed pathophysiologic mechanisms underlying progressive cortical thinning in epilepsy are either the direct or indirect effects of seizures or the consequences of spreading neuronal and synaptic abnormalities in pathological epileptic networks (Galovic, van Dooren, *et al.*, 2019). Seizures and synaptic alterations might lead to excitotoxicity, metabolic stress, inflammation (Vezzani *et al.*, 2011), and cell death (Sutula *et al.*, 2003). We hypothesised that successful surgical removal of a sufficient portion of the epileptic network leading to postoperative seizure freedom would, thus, reduce these pathological processes and would prevent further progressive cortical thinning, as has been confirmed by our results.

The key result and novel finding of the current study is that cortical thinning was significantly lessened after epilepsy surgery compared to before the surgery (**Figure 1C, Figure 2**). The overall thinning rate was normalised postoperatively to a level comparable with healthy volunteers (**Figure 1C**). After right temporal lobe resection, there were no focal areas of progressive thinning that exceeded the effects of normal aging (**Figure 1B right**). After left anterior temporal lobe resections, the continuation of progressive atrophy was reduced but there still remained foci of progressive thinning in the ipsilateral posterior temporal lobe, cingulate gyrus and precuneus (**Figure 1B left, Figure 3**). This could be the consequence of ongoing Wallerian degeneration in nerve bundles disconnected during surgery. Alternatively, it could be explained by surgical failure in a portion (59%) of these subjects, who had continued epileptic activity and seizures that may be associated with ongoing neurodegeneration. This explanation is supported by the observation that postsurgically accelerated atrophy was not observed in patients who became completely seizure-free after surgery (**Figure 4B**). Thus, accelerated cortical thinning observed in patients with ongoing seizures after surgery may be driven by continuing epileptic activity due to the incomplete removal of the epileptic focus. Whereas those with continued postoperative seizures had small areas of accelerated thinning (**Figure 4A**), seizure-free subjects did not have any detectable thinning beyond normal aging (**Figure 4B**). In other words, successful surgery leading to long-term seizure-freedom might be required to completely normalise the rate of cortical thinning, whereas failed surgery with ongoing postoperative seizures might only achieve a partial reduction in cortical thinning.

The finding of reduced cortical thinning after surgery was largely consistent between the two independent groups with left and right TLE, adding support to the robustness of this result. However, there were also relevant differences between left and right temporal surgery. We detected more pronounced effects on cortical structure after removal of the left compared to the right temporal lobe (**Figure 2**). This could be due to the larger sample size and statistical power of the left (n=47) vs. right (n=38) TLE groups. In addition, TLE in the left, usually language dominant, hemisphere is associated with more extensive presurgical structural alterations (**Figure 1A**) (Galovic, van Dooren, *et al.*, 2019; Whelan *et al.*, 2018). Left TLE shows more widespread cortical thinning (Whelan *et al.*, 2018) and abnormal microstructural integrity (Focke *et al.*, 2008) compared to right TLE. Left TLE has an earlier onset of seizures (Blümcke *et al.*, 2017), suggesting a more severe disease with more widespread network affection on the left. Thus, removal of the epileptic focus on the left might have more marked postoperative effects. In contrast, removal of the right anterior temporal lobe might have a smaller impact, because progressive cortical thinning is less pronounced preoperatively.

Interestingly, most of the effects after left temporal lobe resection were observed in the right hemisphere (**Figure 2A, Figure 3**), potentially suggesting restitution of normal cortical structure and function in the contralateral hemisphere, that might have been presurgically affected by the spread of epileptic activity. On the other hand, these changes could reflect structural compensation as a physiologic adaptation after removal of the left temporal lobe. Likewise, increases in fractional anisotropy of white matter networks after left-sided resections were thought to be linked to plasticity relevant to language function (Yogarajah *et al.*, 2010). In a similar manner, areas of focal hypertrophy after left- (right supramarginal gyrus and superior parietal lobule, **Figure 1B left**) and successful right-sided (right postcentral gyrus, **Figure 4B right**) resections could also reflect structural compensation. The underlying mechanisms could represent reversal of a functional (Dahal *et al.*, 2019) or metabolic (Spanaki *et al.*, 2000) disruption leading to secondary synaptogenesis.

Consistent with our findings, one previous study found relative postsurgical increases in grey matter concentration, particularly in seizure-free cases and in the hemisphere contralateral to the resection (Yasuda *et al.*, 2010). Postsurgically normalised cortical thinning in the ipsilateral pericentral areas observed in our study (**Figure 2**) is paralleled by previously described postoperative increases in fractional anisotropy in the ipsilateral internal and external capsules and corona radiata after anterior temporal lobe removal, interpreted as post-operative plasticity after the insult of surgery (Winston *et al.*, 2014; Yogarajah *et al.*, 2010). Compensatory functional reorganisation of language and memory networks has been observed after anterior temporal lobe resection (Bonelli *et al.*, 2013; Sidhu *et al.*, 2016). Efficient reorganisation was associated with plasticity in the contralateral hippocampus, insular, and anterior cingulate cortex (Sidhu *et al.*, 2016).

This study has limitations. Firstly, our findings only apply to the first year after surgery. It is unclear, whether the beneficial effects of surgery on brain structure extend beyond this timeframe, warranting further long-term studies. Studies of individuals 5-10 years after temporal resection are needed to determine if progressive atrophy is halted in the longer-term after surgery. Our results only apply to standard anterior temporal lobe resections and future research will need to determine whether they can be extended to other types of surgery.

Secondly, data from patients with epilepsy and healthy volunteers were acquired on different 3T MRI scanners. As has been discussed in our previous study (Galovic, van Dooren, *et al.*, 2019), the statistical analyses focused on within-individual changes and all individuals were rescanned on the same equipment, minimising the effect of between-cohort differences. Moreover, all groups were comparable for baseline characteristics and the statistical analyses were additionally adjusted for relevant covariates. Post hoc analyses (Online Supplement, section 5) showed that our results cannot be explained by a reduced sensitivity to detect cortical thinning in healthy volunteers or postsurgical patients compared with presurgical patients. A significantly reduced cortical thinning after successful surgery (**Figure 2**), which is the main result of the study, was not affected by scanner differences.

Thirdly, pre- and postsurgical cortical thinning was analysed in two independent groups and the results would be more robust if all participants had paired pre- and postsurgical scans. However, a sensitivity analysis in eight patients with both pre- and postsurgical scans replicated similar results to the overall analysis. Both the main (**Figure 2A**) and the sensitivity (**Figure 3**) analyses showed a highly concordant reduction of progressive cortical thinning in the right hemisphere, particularly in the right posterior temporal, parietal, and occipital cortices, right supramarginal gyrus, right cingulate cortex, right frontal opercular cortex, and right precentral and superior frontal gyri. The only area of reduced atrophy in the main analysis, that was not replicated in the sensitivity analysis, was in the left superior pre- and postcentral gyri. On the other hand, the sensitivity analysis also found more progressive cortical thinning in the left supramarginal and superior temporal gyrus, possibly pointing to ongoing Wallerian degeneration after surgery.

Fourthly, a limitation inherent in most epilepsy studies is the possible influence of AED intake in patients compared with healthy volunteers. There was no difference in the pre- and postsurgical number of AEDs, because medication withdrawal is not usually commenced during the first postoperative year at our centre. Additionally. it is unlikely that our results could be explained by differences in medication only because we did not find any association of AED load with progressive atrophy before or after surgery (Online Supplement, section 6).

Fifthly, our epilepsy cohort was single-centre. Nevertheless, it is likely that the results are generalizable to other centres performing standard anterior temporal lobe resections, as established recommendations for this surgical procedure were followed.

Sixthly, some of the secondary findings were anatomically not immediately intuitive. Focal left temporo-occipital cortical thinning after unsuccessful right temporal lobe resection (**Figure 4A**) may reflect ongoing neurodegeneration due to incomplete removal of the epileptic focus. Focal right postcentral cortical thickening after successful right temporal lobe resection (**Figure 4B**) may in turn reflect normalisation and consequent structural hypertrophy in this area after removal of the epileptic focus. These observations may be related to the small sample size of subgroup analyses and the findings may need to be replicated in larger studies.

Lastly, immediate effects of surgery such as brain shift or Wallerian degeneration may interfere with image pre-processing, particularly during the first postoperative weeks. By studying the interval from 3 to 12 months after surgery we reduced the effect of these immediate changes on our findings. In addition, we applied a dedicated preprocessing pipeline and masked the resulting images with a safety margin to eliminate any residual effect. The spatial pre-processing accuracy was comparable between all groups, making it unlikely that the results could be explained by image misregistration.

To conclude, we provide evidence that epilepsy surgery in TLE, especially if the individuals become seizure free, abrogates the accelerated cerebral atrophy associated with refractory TLE. Successful resective surgery is, so far, the first procedure that might prevent further neurodegeneration in epilepsy. This consideration provides a further incentive to consider surgical treatment earlier in individuals with refractory TLE, ideally after two appropriate AEDs have been tried (Haneef *et al.*, 2010).

Declaration of interests

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Figures

Figure 1: *Progressive cortical thinning in pre- and postsurgical epilepsy and healthy volunteers.*

Comparison of progressive cortical thinning in pre- (panel A) and postsurgical (panel B) epilepsy cohorts with healthy volunteers. Significant clusters ($p<0.05$, correction for multiple comparisons using random field theory) and the mean resection extent are superimposed on hemispheric surface templates. Blue clusters indicate progressive atrophy, red colours indicate progressive hypertrophy, resection extent is displayed in shades of purple. FWE indicates familywise error.

Panel C shows regional cortical thickness estimates and the predicted rate of regional cortical thinning in healthy controls (grey), pre- (blue) and postoperative (orange) TLE patients. Each scan is represented by a dot and scans corresponding to the same patient are connected by a thin line. The three thick lines are linear regression lines of mixed effects models and their slope represent the estimated rate of cortical thinning in each group. Because mixed effects models were fitted with a variable intercept, all linear regression lines were adjusted to have the same intercept. The graph shows an accelerated rate of cortical thinning in preoperative TLE patients compared to healthy controls. This rate is largely normalised in postoperative TLE patients. The analysed regions were defined as those areas that showed significant cortical thinning before surgery in panel A.

Figure 2: *Direct comparison of progressive cortical thinning after vs. before surgery.*

Comparison of progressive cortical thinning in postsurgical vs. presurgical patients with left (panel A) or right (panel B) temporal lobe epilepsy. Significant clusters ($p<0.05$, correction for multiple comparisons using random field theory) and the mean resection extent are superimposed on hemispheric surface templates. Blue clusters indicate accelerated atrophy after surgery, red colours indicate reduced atrophy after surgery, resection extent is displayed in shades of purple.

Figure 3: *Direct within-subject comparison of progressive cortical thinning after vs. before surgery.*

Comparison of within-subject changes to progressive cortical thinning in a subgroup of eight patients with left TLE who had both pre- and postsurgical paired scans. Significant clusters ($p<0.05$, correction for multiple comparisons using random field theory) and the mean resection extent are superimposed on hemispheric surface templates. Blue clusters indicate accelerated atrophy after surgery, red colours indicate reduced atrophy after surgery, resection extent is displayed in shades of purple.

Figure 4: *Progressive cortical thinning in non-seizure-free and seizure-free postsurgical epilepsy patients vs. healthy volunteers.*

Comparison of progressive cortical thinning in non-seizure-free and seizure-free postsurgical epilepsy patients with healthy volunteers. Significant clusters ($p<0.05$, correction for multiple comparisons using random field theory) and the mean resection extent are superimposed on hemispheric surface templates. Blue clusters indicate accelerated atrophy after surgery, red colours indicate reduced atrophy after surgery, resection extent is displayed in shades of purple.

Tables

Table 1: *Baseline characteristics*

	TLE presurgical (n = 29)	TLE postsurgical (n=56)	Healthy volunteers (n=124)	P value
Gender				
Female	15 (52%)	36 (64%)	76 (61%)	0.51
Male	14 (48%)	20 (36%)	48 (39%)	
Age				
Age mid-scan *(years)*	38 ± 11	39 ± 12	38 ± 17	0.88
Age at seizure onset *(years)*	16 ± 12	13 ± 10	--	0.27
Age at surgery *(years)*	41 ± 11	39 ± 12	--	0.64
Duration of epilepsy at surgery *(years)*	25 ± 12	26 ± 14	--	0.66
Presurgical seizures				
Focal aware	12 (41%)	30 (54%)	--	0.36
Focal impaired awareness	28 (97%)	54 (96%)	--	1.00
Focal to bilateral tonic-clonic	21 (72%)	97 (82%)	--	0.59
Focal impaired awareness frequency *(per month)*	8 ± 7	26 ± 130	--	0.47
Focal to bilateral tonic-clonic frequency *(per month)*	0.8 ± 1.8	0.6 ± 1.8	--	0.68
Side of surgery				
Right	12 (41%)	24 (43%)	--	1.00
Left	17 (59%)	32 (57%)	--	
Pathology				
Hippocampal sclerosis	20 (69%)	44 (79%)	--	0.43
Dysembryoplastic neuroepithelial tumor	5 (17%)	4 (7%)	--	0.26
Cavernoma	1 (3%)	2 (4%)	--	1.00
Other	7 (24%)	9 (16%)	--	0.39
Surgical outcome				
Seizure free after surgery (ILAE Class Ia)	12 (41%)	23 (41%)	--	1.00
Other				
Number of antiepileptic drugs at surgery	3 ± 1	3 ± 1	--	0.49
History of a precipitating injury*	3 (10%)	4 (7%)	--	0.69
History of childhood febrile convulsions	4 (14%)	9 (16%)	--	1.00
History of depression	9 (32%)	19 (34%)	--	1.00
History of psychosis	3 (11%)	4 (7%)	--	0.68
History of anxiety disorder	3 (11%)	9 (16%)	--	0.74
Preprocessing accuracy *(Dice coefficient)*	0.96 ± 0.02	0.96 ± 0.01	0.95 ± 0.03	0.18

Data displayed as N (%) or mean ± standard deviation. Data analysed with Fisher's exact test for nominal variables or with one-way ANOVA for scalar variables. * Most commonly reported precipitating injuries were a history of meningitis or traumatic brain injury.

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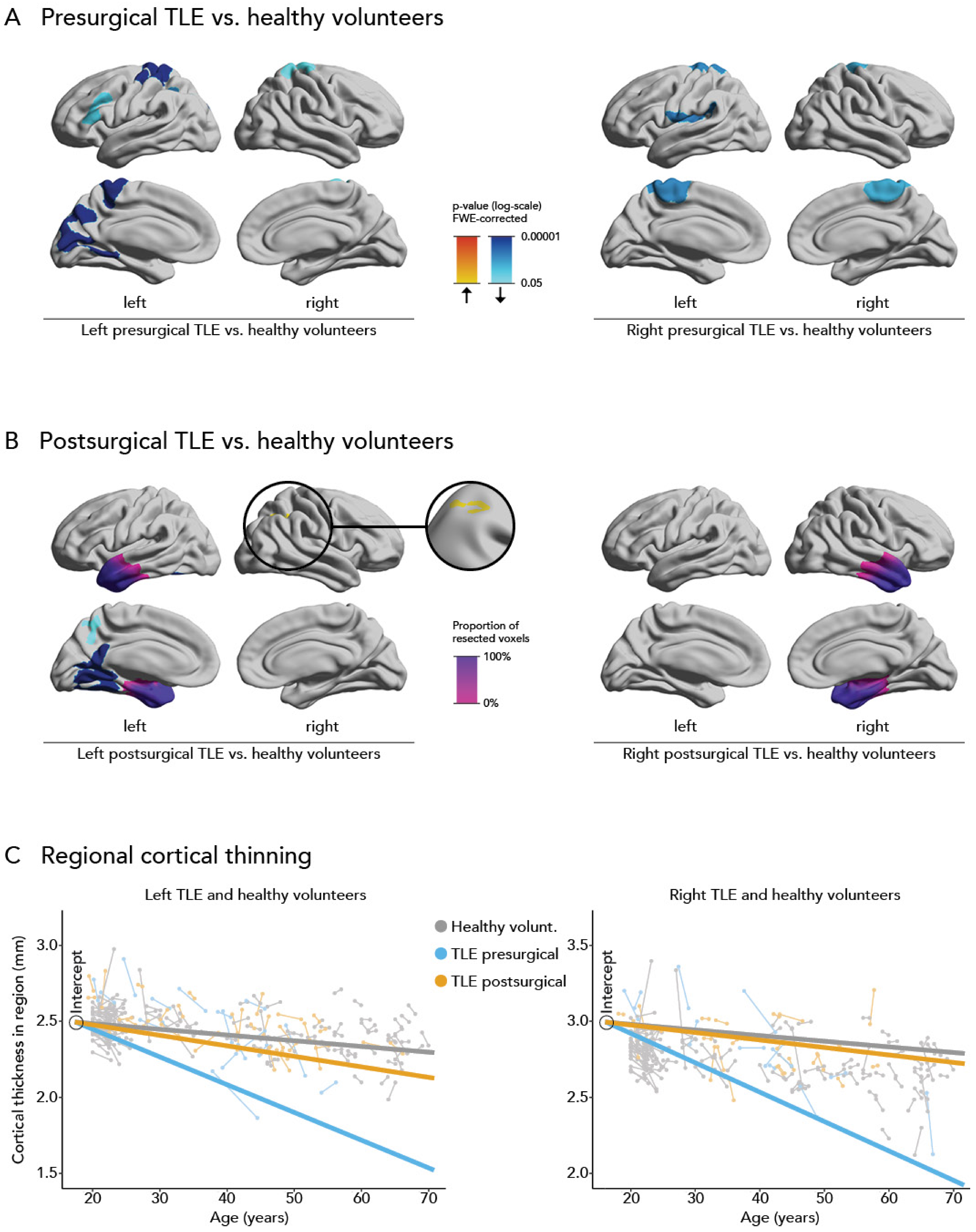
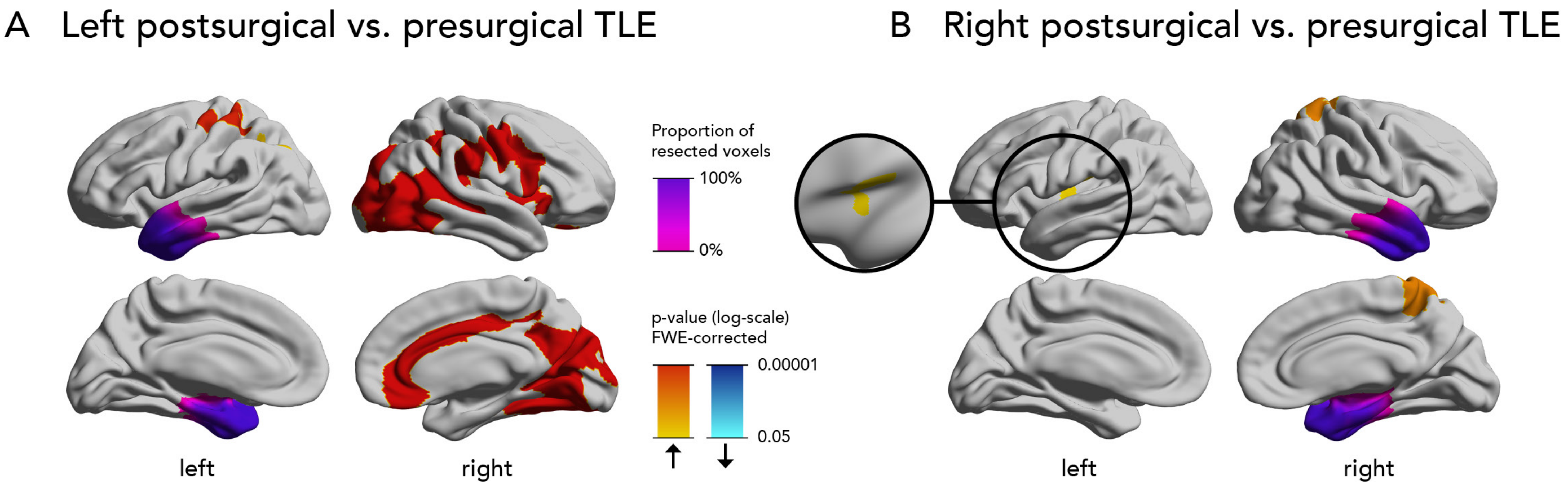
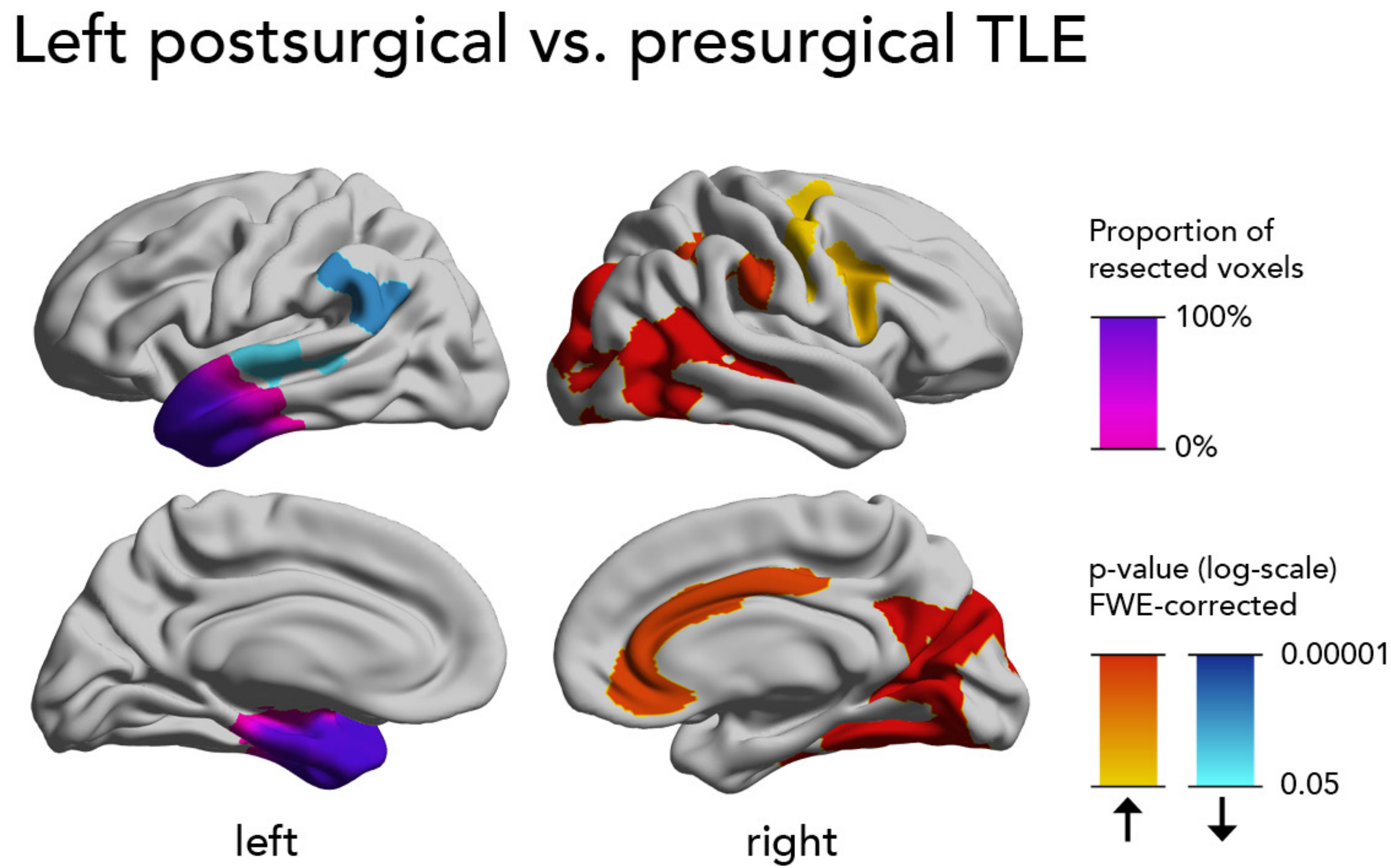
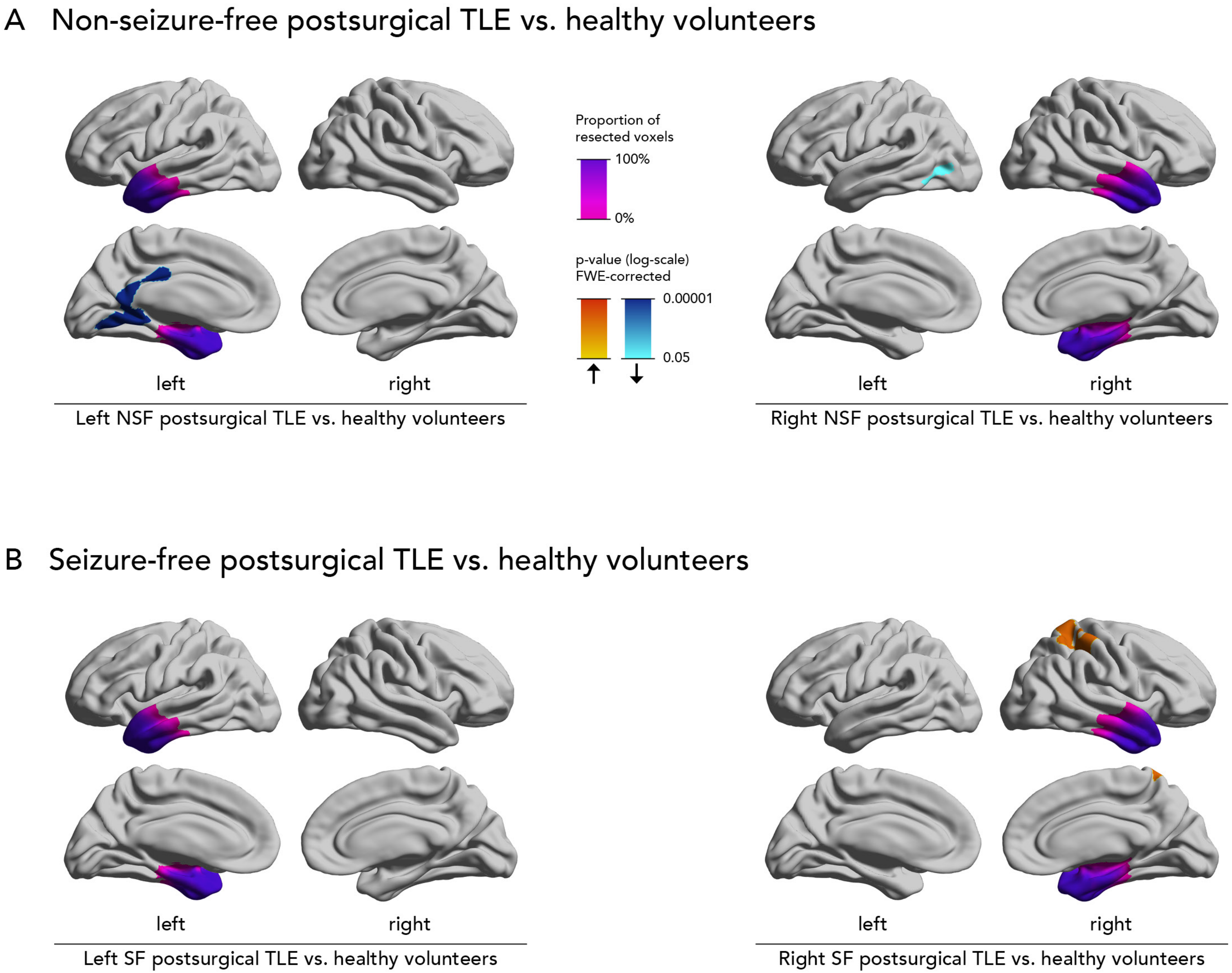


A Presurgical TLE vs. healthy volunteers
left
right
Left presurgical TLE vs. healthy volunteers
p-value (log-scale)
FWE-corrected
0.00001
0.05
left
right
Right presurgical TLE vs. healthy volunteers
B Postsurgical TLE vs. healthy volunteers
Proportion of
resected voxels
100%
0%
left
right
Left postsurgical TLE vs. healthy volunteers
left
right
Right postsurgical TLE vs. healthy volunteers
C Regional cortical thinning
Left TLE and healthy volunteers
Healthy volunt.
TLE presurgical
TLE postsurgical
Intercept
Cortical thickness in region (mm)
3.0
2.5
2.0
1.5
20
30
40
50
60
70
Age (years)
Right TLE and healthy volunteers
Intercept
3.5
3.0
2.5
2.0
20
30
40
50
60
70
Age (years)



A Left postsurgical vs. presurgical TLE
B Right postsurgical vs. presurgical TLE
Proportion of resected voxels
100%
0%
p-value (log-scale) FWE-corrected
0.00001
0.05
left
right
left
right


Left postsurgical vs. presurgical TLE
Proportion of resected voxels
100%
0%
p-value (log-scale) FWE-corrected
0.00001
0.05
left
right


A Non-seizure-free postsurgical TLE vs. healthy volunteers
Proportion of resected voxels
100%
0%
p-value (log-scale) FWE-corrected
0.00001
0.05
left
right
Left NSF postsurgical TLE vs. healthy volunteers
left
right
Right NSF postsurgical TLE vs. healthy volunteers
B Seizure-free postsurgical TLE vs. healthy volunteers
left
right
Left SF postsurgical TLE vs. healthy volunteers
left
right
Right SF postsurgical TLE vs. healthy volunteers